



IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of: HOFFMAN, Arnold et al. Examiner: James D.
Anderson
Application No.: 10/621,326 Art Unit: 1614
Filed: 4/17/2004
For: REDOX THERAPY FOR TUMORS

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DECLARATION UNDER RULE 1.132

The Honorable Commissioner
of Patents and Trademarks
Box Non-Fec Amendment
Washington, DC 20231

Sir:

I, Arnold Hoffman, declare that:

1. I currently reside at 5 Hagra St. Rehovot, Israel. I have personal knowledge of the facts set forth herein.
2. I am familiar with the Office Action dated 18 March 2009, which the Patent and Trademark Office mailed in regard to the above-captioned patent application. In response I declare and state as follows:
3. In the last few decades, large amounts of resources and time have been invested in an effort to develop a systemic, safe/non-DNA-damaging but effective therapy for treating cancer patients. There are tens, if not hundreds, of prior art agents and combinations that are effective, in vitro, against cancer cells. However, the in vivo results

of these agents or combinations are disappointing.¹ The state of the present art remains stymied by its inability to obtain, in vivo, the high level of effectiveness against cancer cells observed in vitro. Clearly, it is not the agents that are at fault, because the in vitro results demonstrate that these agents, such as DSF and curcumin, are capable of effectively killing these cancer cells. The major cause of failure is the lack of awareness in the prior art of the nature of the intrinsic in vivo impediment to effectiveness, and so the prior art does not (and cannot) teach or suggest a therapy for systemically treating cancer patients until the nature of this impediment is identified and overcome.

4. The above-captioned patent application discloses, with respect to a Redox Therapy, the nature of the aforesaid impediment and how to overcome it. The subject patent teaches that this impediment is associated with the intermittent administration of the agent that characterizes in vivo administration. In vitro, the agent is in continuous contact with the cancer cells for the duration of the treatment so that the dephosphorylated state of RB is continuously maintained for the complete incubation period. The in vitro effectiveness of DSF by itself against cancer cells such as MX-1 is at

¹ NCI researchers have reviewed the state of the art that existed a couple of years after the time the subject patent was filed (Zuben et al. Mol. BioSystems 1: 127-134 2005). Below are quotes from this Review.

"Systemic chemotherapy is extensively used as the treatment of choice in cancers that are metastatic; i.e. approximately 50% of all cancers. However, no more than 10% of patients are cured by chemotherapy."

"The last decade has seen numerous reports suggesting that DSF may play a very useful role in the treatment of human cancers."

"In addition, to inducing apoptosis, DSF has been shown to inhibit the growth of cancer cells both in vivo and in vitro."

"While combinations of synergistic compounds have been exploited for decades, these are generally limited to agents known to be effective in a therapeutic area or to agents with a clear rationale for the combination."

"It is interesting that of the 435 possible two-component combinations, only six effective combinations emerge, of which two have disulfiram."

"Reviewing the status of cancer research over the past 25 years, Hanahan and Weinberg describe the scientific literature as 'complex beyond measure' but argue that new progress will now come from being able to understand cancer in terms of a small number of underlying principles".

From the above it would appear that at least some in the current art recognize that several years of effort exploring presumably obvious directions of research, have not succeeded.

the maximum detectable limit, so that no in vitro synergistic effect as a result of adding the other agents is possible.²

5. Cen et al. and Kennedy et al. (cited by the examiner), show a very high level of in vitro effectiveness of DSF against melanoma cells. In vivo, however, the art as yet has not discovered how DSF by itself, or in combinations with other agents, can provide adequately effective results to treat cancer patients. The subject patent teaches that in vivo, DSF is not adequately effective because intermittent DSF administration does not provide for continuously maintaining the dephosphorylated state of RB for between 15-75 hours, because, between administration periods, the RB can become phosphorylated, promoting cell proliferation. The subject application teaches that an effective Redox Therapy for treating cancer patients requires a treatment that provides in vitro conditions for the in vivo therapy; i.e. continuously maintaining the dephosphorylated state of RB from 15-75 hours. This requires maintaining the dephosphorylated state of RB between administration periods. The subject application teaches that this can be achieved by calibrating the frequency of administration of the agent to the duration of the effectiveness of the agent to continuously maintain the dephosphorylated state of RB between administration periods. The duration of effectiveness of these agents to maintain the dephosphorylated state of RB can be extended by adding other agents that deactivate the GR and/or the gamma-GCS enzymes. The combination of the four agents disclosed in the subject patent can provide in vivo synergy when administered at a particular frequency.

6. Conventional practice in evaluating agents and combinations comprises the

². The present inventors' in vitro results show the highest level of effectiveness against MX-1 cancer cells for both DSF by itself as well as for DSF in combination with the other 3 agents.

following steps;

- (1) evaluate in vitro, effectiveness of agent against cancer cells;
- (2) if effective go to step (4)
- (3) if not adequately effective, search for synergistic combinations of agents;
- (4) evaluate (2) or (3) in vivo via intermittent administration to cancer -

bearing animals.

As the combination of these agents to DSF does not/cannot enhance the already excellent in vitro results, one skilled in the art would skip from step (2) to step (4), and the addition of these other agents will not be explored. Consequently, discovery of the 4-agent combinations disclosed in the subject patent would not be obvious to one in the art.

6. I am familiar with the Marikovsky, Sharma, Johnson, Bailey references cited as a basis for rejection of the subject patent application on grounds of "anticipation", as well as my own WO 02/056823 application. In each case the examiner attributes the reference with anticipating the claimed "pharmaceutically effective dosage." However, current claim 26 requires a combination of E-increasing agents disulfiram and curcumin, together with enzyme deactivating agents BCNU and BSO, *and the pharmaceutically effective dosage further comprises a calibrated administration frequency* to continuously maintain said decreased $[GSI-1]2/[GSSG]$ ratio in the malignant cells and consequently, continuously maintain said dephosphorylated state of the RB in said cancer cells, within a range of from 15 to 75 hours in order to span at least one cell cycle. None of these cited references teach or suggest the combination of these agents, plus a pharmaceutically effective dosage comprising a calibrated administration frequency to continuously maintain the dephosphorylated state of RB (high E) for 15-75 hours.

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I further declare that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or by both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the above referenced patent.

Signature:


Arnold Hoffman

Date: June 16, 09